CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Use of Fixed-Dose Regimens in Chronic Lymphocytic Leukemia

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H&O What fixed-dose regimens are in use in chronic lymphocytic leukemia (CLL)?

AK Fixed-duration regimens have been used for a long time in patients with CLL. Fludarabine, cyclophosphamide, and rituximab (FCR) used to be the regimen of choice for young, fit patients; bendamustine plus rituximab (BR) became the regimen of choice for older, fit patients; and chlorambucil plus the anti-CD20 monoclonal antibody obinutuzumab (Gazyva, Genentech) used to be the regimen of choice for older patients. Those were the fixed-duration regimens of origin. More recently, the development of highly effective targeted agents led to approval of the BCL2 inhibitor venetoclax (Venclexta, AbbVie), which can be given as a 12-cycle fixed-duration treatment in combination with obinutuzumab and continuous treatment with a Bruton tyrosine kinase (BTK) inhibitor. Very recently, a combination of venetoclax and ibrutinib (Imbruvica, Pharmacyclics/Janssen) became evaluable as a fixed-duration option (15 cycles).

As effective as BTK inhibitors are, these are expensive drugs that become even more expensive when patients remain on them until they experience relapse. Another disadvantage of BTK inhibitors is the risk of serious side effects, which can include cardiac toxicity, bleeding, and vulnerability to infections. Using these agents upfront also means that we lose BTK as a target as soon as a patient experiences relapse. These disadvantages led to interest in the use of BTK inhibitors on a fixed-duration basis. The first such study was of the combination of venetoclax plus ibrutinib (Imbruvica, Pharmacyclics/Janssen), which had been approved in Canada and Europe on the basis of results of the phase 3 GLOW study. More recently, the AMPLIFY study, which was presented at the most recent American Society of Hematology Annual Meeting, supported the use of doublet therapy with fixed-dose acalabrutinib (Calquence, AstraZeneca) plus venetoclax (AV) as well as triplet therapy with fixed-dose acalabrutinib, venetoclax, and obinutuzumab (AVO).

In the relapsed setting, the MURANO study showed that a combination of venetoclax and rituximab is effective.

H&O What was the impetus for the AMPLIFY trial?

AK In light of what we know about the biology of CLL, it makes a lot of sense to combine acalabrutinib and venetoclax. BTK inhibitors, whether they be ibrutinib, acalabrutinib, or zanubrutinib (Brukinsa, BeiGene), are highly efficient at preventing depleted tumor cells from traveling to the lymph nodes, which is where they are recharged before returning to the bloodstream. I like to think of each tumor cell as a Formula One racing car that begins to break down after a long drive and needs to enter the pit lane for repairs. BTK inhibitors essentially close off the pit lane, leaving the tumor cells vulnerable when they are already at their weakest. This makes the cells much more sensitive to venetoclax-mediated killing. In theory, this is a very pragmatic approach to attacking CLL. Another advantage of the approach is that all treatment is given orally.

BTK inhibitors can cause cardiac toxicity, hypertension, and bleeding disorders. We chose to study acalabrutinib because this second-generation BTK inhibitor seems to have a better toxicity profile than ibrutinib's, at least when used as monotherapy.

H&O Could you describe the design of AMPLIFY?

AK AMPLIFY is an open-label phase 3 trial of adults with treatment-naive CLL who have an Eastern Cooperative Oncology Group performance status of 0 to 2 and who do not have del(17p) or a *TP53* mutation. We were able to enroll 867 patients, which makes this a fairly large study for CLL. Patients were randomized in a 1:1:1 ratio to receive 14 cycles of AV, 14 cycles of AVO, or 6 cycles of investigator's choice of FCR or BR. This is one of the last studies to have a chemoimmunotherapy control arm. Acalabrutinib was given orally for 14 cycles, venetoclax was given orally from cycles 3 to 14 with a 5-week dose ramp-up to reduce the risk of toxicities from tumor lysis, obinutuzumab was given intravenously from cycles 2 through 7, and chemoimmunotherapy was given from cycles 1 through 6.

The median age of the patients in this study was 61 years, so this was a relatively young population. More than 60% of the patients came from Europe, and fewer than 20% came from North America. We stratified patients by *IGHV* mutation status because immunoglobulin heavy-chain variable region gene (*IGHV*)-unmutated disease is more aggressive and less sensitive to chemoimmunotherapy; nearly 60% of the patients had unmutated *IGHV* status.

H&O What were the results of the trial?

AK Looking at the intention-to-treat population, the progression-free survival (PFS) rate at 36 months as assessed by the independent review committee (IRC) was highest in the AVO population (83.1%), second highest in the AV population (76.5%), and lowest in the chemoimmunotherapy population (66.5%).

As expected, the differences between the AVO/AV arms and the chemoimmunotherapy arm were largest among the patients with unmutated *IGHV*. Among these patients, the IRC-assessed PFS rate at 36 months was 82.8% in the AVO group, 68.9% in the AV group, and 56.8% in the chemoimmunotherapy group. By contrast, in the group with mutated *IGHV*, the IRC-assessed PFS rate at 36 months was 83.6% in the AVO group, 86.0% in the AV group, and 79.9% in the chemoimmunotherapy group.

This study was hit very hard by COVID-19, which is especially risky for patients who have CLL. We saw a COVID-specific mortality rate of 8.7% in the AVO arm, 3.4% in the AV arm, and 7.2% in the chemoimmunotherapy arm. Most of the patients in the chemoimmunotherapy arm had completed treatment when the pandemic hit, but treatment was ongoing in the AVO and AV arms. So the question is, how did COVID affect our results?

First, it is very important to know that because patients were being treated early in the pandemic, only slightly more than half of them received a COVID vaccine during the treatment period. This is a source of potential bias in the study.

Regarding our analysis, we wanted to see if some arms were more affected by COVID than others. After we censored for COVID deaths, the 36-month PFS rate was 91.5% in the AVO group, 78.8% in the AV group, and 72.0% in the chemoimmunotherapy group. These numbers were a little bit better than they were without the censoring, but we saw roughly the same pattern as before.

As far as overall survival (OS) is concerned, the 36-month OS rate was statistically significantly longer with AV than with chemoimmunotherapy, at 94.1% vs 85.9%. The 36-month OS rate with AVO was 87.6%, which was not statistically significantly higher than the rate with chemoimmunotherapy. After censoring for COVID deaths, however, the 36-month OS rates were once again roughly the same for AVO and AV: 96.2% and 97.5%. This makes sense because obinutuzumab depletes B cells even more than rituximab does, so that the body is unable to manufacture antibodies against COVID in response to either vaccination or infection. As a result, the addition of obinutuzumab to treatment decreased OS even though it increased PFS.

So which results are more representative—the ones for the entire group or the ones censored for COVID deaths? We already know that patients who have CLL are highly vulnerable to infections. Should we then remove COVID deaths from the equation, or should we appreciate the value of knowing how infectious diseases can affect results? In the Netherlands, we use the term "yellow canary" to refer to an unexpected event that directs our attention to something important. Were the COVID deaths that yellow canary?

H&O How did measurable residual disease (MRD) status affect the response to treatment?

AK We know from studies with chemotherapy that patients who have undetectable MRD, with a cutoff of 10^{-4} at the end of treatment, do much better than patients who still have detectable MRD at the end of treatment. We have learned that the same is true for venetoclax—that patients who have undetectable MRD at the end of treatment do much better. When it comes to venetoclax plus ibrutinib, the GLOW study also showed that patients with undetectable MRD did somewhat better than those who had detectable MRD, but the difference was less pronounced, especially among patients who had mutated *IGHV*. The relevance of undetectable MRD was much greater in patients who had unmutated *IGHV*.

All of this is to remind us that we do not yet understand exactly how valuable and how predictive MRD may be in this setting. At 3 months after the end of treatment in the intention-to-treat analysis of the AMPLIFY study,

undetectable MRD was noted in 65.0% of patients in the AVO arm, 29.9% of patients in the AV arm, and 51.0% of patients in the chemoimmunotherapy arm. The numbers were better in an analysis of just the evaluable patients, however, with undetectable MRD noted in 94.4% of patients in the AVO arm, 38.0% of patients in the AV arm, and 77.9% of patients in the chemoimmunotherapy arm.

The PFS and OS numbers were all very good in these first primary outcome data, but it is important to have longer-term follow-up for this kind of treatment to learn whether MRD status really matters.

H&O Could you describe the side effects seen in the 3 groups?

AK We saw any-grade neutropenia in 40.1% of patients in the AVO arm, 30.9% of patients in the AV arm, and 38.2% of patients in the chemoimmunotherapy arm. Grade 3 or higher neutropenia occurred in 35.2% of patients in the AVO arm, 26.8% of patients in the AV arm, and 32.4% of patients in the chemoimmunotherapy arm. Most cases of neutropenia occurred without fever, which is important because febrile neutropenia is what we really worry about. Grade 3 or higher febrile neutropenia occurred in 2.5% of patients in the AVO arm, 1.7% of patients in the AV arm, and 9.3% of patients in the chemoimmunotherapy arm.

We also worry about cardiac events with CLL treatment, but the rate of atrial fibrillation was very low in the AV and chemoimmunotherapy groups. Atrial fibrillation occurred in 2.1% of patients in the AVO group, 0.7% of patients in the AV group, and 0.8% of patients in the chemoimmunotherapy group. The numbers are less than what we see with first-generation BTK inhibitors.

We also worry about high blood pressure with BTK inhibitors, but the rate of hypertension was low in all the groups. The rate of all-grade hypertension was 3.9% with AVO, 4.1% with AV, and 2.7% with chemoimmunotherapy.

Bleeding is something else we worry about with BTK inhibitors, but the rate of grade 3 or higher major hemorrhage was 2.1% with AVO, 1.0% with AV, and 0.4% with chemoimmunotherapy.

Grade 3 or higher infections occurred in 23.6% of patients in the AVO group, 12.4% of patients in the AV group, and 10.0% of those in the chemoimmunotherapy group.

The last adverse events I want to mention are second primary malignancies, which are important because they have always been related to FCR chemoimmunotherapy. Fortunately, the rates were low in this study. The rate of second primary malignancies excluding nonmelanoma skin cancer was 2.5% for AVO, 2.7% for AV, and 0.4% for chemoimmunotherapy. These are very low rates, but we may see more cases of second primary malignancies over time.

H&O Do you expect that both AV and AVO will receive US Food and Drug Administration (FDA) approval, or just AV?

AK We saw that the European Medicines Agency (EMA) was willing to approve the use of venetoclax/ibrutinib on the basis of results of the GLOW study, whereas the FDA did not approve this combination because of the increase in toxicities seen with venetoclax/ibrutinib vs chlorambucil/obinutuzumab. The results of the AMPLIFY study were also complicated by the COVID pandemic, and it is unclear how the FDA will view the incidence of COVID deaths. Therefore, it is difficult for me to anticipate how the FDA will rule, but it is possible that the manufacturer will request approval only for the AV combination. As for me, I think that with the relatively short follow-up until now, the increase in toxicity with triplet therapy vs doublet therapy outweighs the potential benefits. Given the results we have seen so far, I would not choose triplet therapy at this time for my patients.

H&O When can we expect to see new results from AMPLIFY?

AK We still need to take a closer look at MRD in the context of different patient categories, learn more about the toxicities with these regimens, and analyze the effect of COVID vaccination on the study. I hope to see at least some of these data presented at the next European Hematology Association Congress.

Disclosures

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Suggested Readings

Brown JR, Seymour JF, Jurczak W, et al. Fixed-duration acalabrutinib plus venetoclax with or without obinutuzumab versus chemoimmunotherapy for first-line treatment of chronic lymphocytic leukemia: interim analysis of the multicenter, open-label, randomized, phase 3 AMPLIFY trial [ASCO abstract 1009]. *J Clin Oncol*. 2024;42(4)(suppl).

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